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Original research article

Variables altering the impact of respiratory gated CT simulation on planning target volume in radiotherapy for lung cancer

Fawzi Abuhijla[a], *Abdellatif Al-Mousa*[a], *Ramiz Abuhijlih*[a], *Lubna Hammoudeh*[a], *Khalid Dibs*[a], *Adhoob Al-Hammadi*[a], *Taher Abuhejleh*[b], *Jamal Khader*[a,*]

[a] *Department of Radiation Oncology, King Hussein Cancer Center, Amman, Jordan*
[b] *Department of Medical Oncology, King Hussein Cancer Center, Amman, Jordan*

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ABSTRACT

Background: Respiratory gated CT simulation (4D-simulation) has been evolved to estimate the internal body motion. This study aimed to evaluate the impact of tumor volume and location on the planning target volume (PTV) for primary lung tumor when 4D simulation is used.

Methods: Patients who underwent CT simulation for primary lung cancer radiotherapy between 2012 and 2016 using a 3D- (free breathing) and 4D- (respiratory gated) technique were reviewed. For each patient, gross tumor volume (GTV) was contoured in a free breathing scan (3D-GTV), and 4D-simulation scans (4D-GTV). Margins were added to account for the clinical target volume (CTV) and internal target motion (ITV) in 3D and 4D simulation scans. Additional margins were added to account for planned target volume (PTV). Univariate and multivariate analyses were performed to test the impact of the volume of the GTV and location of the tumor (relative to the bronchial tree and lung lobes) on PTV changes by more than 10% between the 3D and 4D scans.

Results: A total of 10 patients were identified. 3D-PTV was significantly larger than the 4D-PTV; median volumes were 182.79 vs. 158.21 cc, $p = 0.0068$). On multivariate analysis, neither the volume of the GTV ($p = 0.5027$) nor the location of the tumor (peripheral, $p = 0.5027$ or lower location, $p = 0.5802$) had an impact on PTV differences between 3D-simulation and 4D-simluation.

Conclusion: The use of 4D-simulation reduces the PTV for the primary tumor in lung cancer cases. Further studies with larger samples are required to confirm the benefit of 4D-simulation in decreasing PTV in lung cancer.

* *Corresponding author.*
E-mail address: jkhader@khcc.jo (J. Khader).

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1. Background

Management of lung cancer is best performed when guided by a decision of a multidisciplinary team. Treatment options include surgery, chemotherapy, radiotherapy and other new modalities, such as targeted therapy and immunotherapy.[1] Radiotherapy can be a curative treatment for lung cancer, and can be used as the sole treatment with or without chemotherapy, but is also considered prior to surgery to improve surgical outcome, or after surgery depending on the surgical margin and the nodal status.[2]

In modern radiotherapy the patient has to pass through different steps in an orderly sequence to receive a radiation treatment, beginning with the radiation oncology clinic, CT simulation, target volume contouring and for the organs at risk, radiation dosimetry planning and quality assurance of the treatment plans followed by radiation treatment. Different techniques have been developed in simulation, planning and dose delivery to improve radiotherapy outcome, these developments require additional software and hardware capabilities to permit proper function.

CT simulation is used to create a replica of the patient's body position and internal anatomy in order to calculate the radiation dose, by obtaining images of the patient using the same position for treatment and the same tools as those used for position fixation during radiotherapy.[3,4]

The 3D CT simulation is a diagnostic CT scanner which has been modified to provide the radiotherapy planning and treatment needs. The main feature of 3D simulators is a large bore or gantry, which allows the use of patient immobilization devices used for radiotherapy. Three dimensional simulation is also supported by a laser alignment system to help in patient positioning.[5]

Respiratory gated or 4D simulation is so named due to the addition of the time factor to the 3D CT simulator scans as a fourth dimension to the image. 4D scans visualize the motion of the intra-thoracic organs as it varies during the breathing cycles through the scanning time.[6,7] Organ motion during simulation scan causes several problems including: image acquisition limitations, treatment planning limitations and radiation delivery limitations. 4D simulation is one of the modalities used to evaluate this motion and overcome the image acquisition and planning limitations.[8]

Previous data showed that the larger the tumor the less motion is seen, and tumor location defined as a peripheral tumor or lower lobe tumor had more chance of intrathoracic motion. However, the effect of these factors combined was not analyzed before to evaluate their effect on the volume change of PTV.[9] The gross tumor volume (GTV) is contoured to include the visualized tumor by radiological imaging. Further expansion is needed to cover the microscopic cancer infiltration into the surrounding area in relation to the tumor which is known as the clinical target volume (CTV) and additional margin for the positioning and setup error known as the planned target volume (PTV). This was explained in detail by the International Commission on Radiation Units (ICRU) report 50.[10] This report defined the GTV, the CTV and PTV as well as the OAR.

There was a further need for additional margin to ensure that the planned target volume is covered due to internal motion. Accordingly; two volumes were added to the list: the internal target volume (ITV), expansion of CTV to account for internal movement (e.g. breathing) and the planning organ at risk volume (PRV) as an expansion of OAR for movement as per ICRU report 62.[11]

Fig. 1 – Respiratory built positioned on the patient.

2. Methods

At the radiotherapy department the CT simulation machine used for 3D scanning is Philips Big Bore CT-sim (32 slices). This CT is equipped with the respiratory belt, retrospective gating scanning protocol and TumorLoc module. The patient breathing pattern is first observed to see which type of a breathing pattern the patient has, abdominal or chest breathing, before fitting the belt.

The respiratory belt is then placed around the patient's chest or abdomen depending on the breathing type, if the patient is a chest breather then the belt is set around the chest, if the patient is an abdominal breather then the belt is set around the patient's abdomen. The belt will display the frequency and depth of breathing through the display and could be seen by the technicians who perform the scanning as seen in Fig. 1.

The patient is then positioned with arms up and knee support, and left lying on the CT-simulation table for a while to calm and restore normal breathing. Orthogonal scouts are taken followed by free-breathing (FB) or 3D scan. The breathing signal is observed to make sure it is uniform and reproducible before starting the retrospective gating scan. The gating scanning protocol is an imaging protocol implemented through the scanning system; through 4D simulation 10 breathing equally-spaced phases are programmed into the retrospective protocol.

The following parameters are important and should be matched between the free breathing scan and each phase-scan: table start and end position and field of view (FOV). Once the scan is over, the images are processed and all 10 phase-scans as well as the FB scan are displayed using the TumorLoc module. The 10 phase-scans represent one breathing cycle starting from 0% scans (start of scanning) usually represent the maximum inhale or inspiration phase and ending at 90% as the 100% is the same as 0% phase. The 50% phases usually represent the maximum exhale or expiration phase.

Since the PTV is the final volume used for radiotherapy dose prescription, the comparison between the changes in volumes by using 4D simulation is done by comparing the PTV through

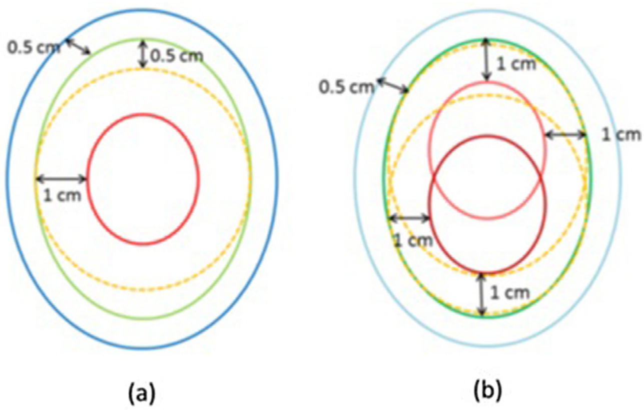

Fig. 2 – Margins used to generate 3D-PTV and 4D-PTV volumes (a) 3D margins: 3D-GTV: red, 3D-CTV: orange, 3D-ITV: green, 3D-PTV: blue, (b) 4D margins: i-GTV: maroon-red, e-GTV: tomato-red, i-CTV and e-CTV: orange, 4D-ITV: dark green, 4D-PTV: light blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3D and 4D simulation scans. After 4D simulation is performed and scanning images are sent to the treatment planning system (TPS). The TPS used at KHCC radiotherapy department is Pinnacle3 V9.10.

Patients who underwent CT simulation for primary lung cancer radiotherapy between 2012 and 2016 using 3D- (free breathing) and 4D- (respiratory gated) institutional protocol treated with conformal radiotherapy (CRT) or intensity modulated radiotherapy (IMRT) were included.

For each patient, gross tumor volume (GTV) was contoured in a free breathing scan (3D-GTV), exhale scan (e-GTV) and inhale scan (i-GTV). The corresponding CTVs (3D-CTV, e-CTV and i-CTV) were created by adding 1 cm in all directions. 3D-internal target volume (3D-ITV) was generated by a 0.5 cm cranio-caudal expansion of 3D-CTV, while 4D-ITV was created by the combination of e-CTV and i-CTV. Subsequently, a 0.5 cm margin was added to generate the 3D-PTV and 4D-PTV, respectively, as shown in Fig. 2. The final 3D-PTV and 4D-PTV were measured using the region of interest (ROI) volume tool in cc.

The following variables were used to assess for potential PTV difference in 3D and 4D simulation: GTV volume, location in relation to lung lobe if lower/middle lobes or upper lobe and location of the primary tumor in relation to the bronchial tree. Tumors within 2 cm expansion from the trachea and main bronchus are defined as central tumors; tumors that are located outside are defined as peripheral tumors.

The volumes of 3D-PTV and 4D-PTV were compared to examine the impact of 4D CT simulation on changes in the volume of PTV. Univariate and multivariate analysis was performed to test the impact of volume and location of GTV on the changes of PTV volume by more than 10% between free breathing and respiratory gated scans.

Statistical analysis. Patient, tumor and treatment characteristics were compiled using descriptive statistics. Continuous variables were described in mean or median (and range) and compared between groups by Student *t*-test. Categorical variables were presented as proportions, and compared with the X^2 test. Multivariate analysis was done using the Logistic Regression model. A significance criterion of $p \le 0.05$ was used in the analysis. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Table 1 – Patients and tumor charactaristics. M: male, F: female, LUL: left upper lober, RLL: right lower lobe, RUL: right upper lobe, RML: right middle lobe, LLL: left lowr lobe. TNM staging as per the AJCC 7th edition.

Age	Gender	Lobe	Location to bronchial tree	TNM stage
84	M	LUL	Peripheral	T1aN0M0
66	M	RLL	Central	T1bN1M0
50	M	LUL	Peripheral	T2aN1M0
63	M	RUL	Central	T2aN0M0
52	M	LUL	Central	T3N2M0
45	F	RML	Central	T3N3M0
66	M	RML	Central	T1bN1M0
79	M	LLL	Peripheral	T1bN2M0
81	M	RUL	Central	T2aN1M0
80	M	LUL	Peripheral	T2aN0M0

3. Results

A total of 10 patients were identified, patients and tumor characteristics are shown in Table 1. The median [range] GTV, i-GTV, e-GTV volumes were 13.55 [1.44–628.66], 13.17 [1.77–627.36], and 12.85 [1.34–630.25] cc, respectively. The 3D-CTV, i-CTV, e-CTV volumes were 86.37 [23.76–1209], 84.97 [25.5–1220.4], and 83.40 [23.36–1224.12] cc, respectively. 3D-ITV and 4D-ITV median [range] volume was 106.06 [3.99–1422.8] and 88.02 [20.51–1338.18] cc, respectively. 3D-PTV was significantly larger than the 4D-PTV; median [range] volumes were 182.79 [58.65– 1861.05] vs. 158.21 [52.76–1771.02] cc, $p = 0.0068$ (Tables 2 and 3).

Factors affecting the difference in volumes between 3D-PTV and 4D-PTV in this study were; GTV volume, tumor location in reference to the lung lobe and tumor location in relation to the bronchial tree.

Table 4 is a univariate analysis for the 3 variables used in the study. Larger tumors were defined as tumors larger than 13.5 cc (GTV median value), showing a tendency toward decrease in 4D-PTV in comparison with 3D-PTV by less than 10%. On the other hand, small tumors equal or less than 13.5 cc showed a tendency for decrease in 4D-PTV in comparison with 3D-PTV by more than 10%. However, none of these findings were statistically significant. Regarding the location in relation to lung lobes; 4 patients had tumor in the lower/middle lobes of whom 2 showed a difference of more than 10%. For the location in relation to the bronchial tree, 5 patients had central tumors, including 2 having a difference of more than 10% for peripheral located tumors, 4 out of 5 showed a difference of more than 10% but not statistically significant.

On multivariate analysis (Table 5), neither the volume of GTV ($p = 0.5027$) nor the location of the tumor (peripheral, $p = 0.5027$ or lower/middle location, $p = 0.5802$) had an in impact on PTV differences between free breathing and respiratory gated scans.

Table 2 – GTV, CTVs, ITVs, PTVs values in 3D and 4D simulation.

GTV Vol (cc)	3D-CTV (cc)	3D-ITV (cc)	e-CTV (cc)	i-CTV (cc)	4D-ITV (cc)	3D-PTV (cc)	4D-PTV (cc)	Difference (%)
1.44	23.8	23.99	23.36	25.5	20.5	58.65	52.32	11
15	82.5	99.6	79.9	81.3	85	167	147.6	12
31.4	130.6	143.1	130.5	130.1	133.7	249	221.9	11
3.4	35.7	46	30.1	34.4	36.9	89	74.6	16
202.4	519.9	581.8	515.4	516	528	821.2	758.2	8
628.7	1209	1422.8	1224.1	1220.4	1338.2	1861.1	1771	5
6.3	57.5	68.2	52.7	47.2	60.7	127.4	115.9	9
12.1	90.2	112.5	86.9	88.6	91	198.6	168.8	15
20.7	104.9	127.5	105.9	106.5	114	216.7	199.9	8
6.6	54.9	67.2	55	56.1	56.5	126.5	110.6	13

Table 3 – Minimum, maximum and median for PTVs in 3D and 4D simulation.

	MIN (cm^3)	MAX (cm^3)	Q1 (cm^3)	Q3 (cm^3)	Median	*p*-value
4D-PTV	52.76	1771.02	110.61	221.87	158.205	0.0068
3D-PTV	58.65	1861.05	126.52	248.96	182.79	

Table 4 – Univariable analysis of factors affecting difference in volume between 3DPTV and 4D-PTV.

Name value	Diff. ≤10%	Diff >10%	Total	*p*-value
GTV (grp)				
GTV ≤13.5 cc	1 (25.0%)	4 (66.7%)	5	0.524
GTV >13.5 cc	3 (75.0%)	2 (33.3%)	5	
Location				
Lower/middle	2 (50.0%)	2(33.3%)	4	1.000
Upper	2 (50.0%)	4 (66.7%)	6	
Central-peripheral				
Central	3 (75.0%)	2 (33.3%)	5	0.524
Peripheral	1 (25.0%)	4 (66.7%)	5	

4. Discussion

Internal motion has been a problem in radiotherapy for a long time, mainly after the evolution of the new high dose targeted radiotherapy. Accounting for this motion using different equipment and methods revealed promising results helping in margin reduction for better OAR avoidance and sparing. These modalities have different scales for additional cost spent for the establishment and maintenance of such modalities. The health sector in developing countries has many challenges in terms of workload and funds availability. Radiotherapy, as one of the main modalities in treating cancer, depends on high cost of equipment and machines, and justifying the cost for this equipment has always been a challenge, as radiotherapy is a highly evolutionary science with new high tech machines appearing on the market every day. Selecting a useful technology at a minimal cost possible is crucial in low income countries.

Four dimensional CT simulation offers a good picture of the tumor range of motion at the time of simulation, and any changes that occur afterwards will not be calculated in the tumor delineation or dose calculations. Lung tumor patients have a higher incidence of lung infection due to the nature of disease and low immunity due to treatment given, such as chemotherapy or targeted therapy. Such infection will cause radiological changes obscuring tumor or altering isodose distribution if change in lung density covers a large lung volume.

Four dimensional CT simulation is considered to be one of the widely used methods for evaluating the internal motion for primary lung cancer. Decrease in PTV is recorded for all tumor sizes of lung cancer, for a large tumor the benefit of minimizing the radiation volume is still important even if the percentage is still small, as large tumors reflect large radiation volumes meaning higher doses received by the normal lung and other OARs.[12] In such cases, even a small decrease in radiation volume would make a difference to have a better radiation treatment plans and avoid serious acute and late side effects for the normal organs surrounding the tumor. This decrease in PTV and sparing of OARs could be reflected in a higher dose delivery as reported by Bai et al.

Previous report by van der Geld et al. showed a decrease in ITV by 52% using 4D CT when compared to virtual fluoroscopy, resulting in avoiding the radiation of unnecessary normal tissue.[13] This decrease in ITV will be reflected in more OAR sparing after the expansion for PTV.

The main objective of this project was to address the need for performing 4D simulation for primary lung tumor radiotherapy and potential benefits over 3D simulation with decreasing the PTV by more than 10%. 6 out of 10 patients showed a decrease in PTV of more than 10% using 4D simulation, but none of the variables studied in this project showed statistical evidence.

Finally, our results were compatible with the previous studies concerning lung tumor's motion. Behavior of lung primary tumor in terms of motion through different breathing cycles

Table 5 – Multivariate analysis of probability of difference in volume between 3DPTV and 4D-PTV.

Effect		Odds ratio estimates	95% CI		*p*-value
Central-peripheral	Central vs peripheral	3.272	0.102	104.804	0.5027
Lower/middle vs upper	Lower/middle vs upper	2.331	0.116	46.818	0.5802
GTV (grp)	GTV ≤13.5 vs GTV >13.5	0.306	0.010	9.786	0.5027

resulted in the decrease of the PTV by using 4D simulation rather than 3D simulation. The limitation of this report is its retrospective nature and the small sample size; therefore, further studies with larger samples is required to confirm the benefit of 4D simulation in decreasing the radiation volumes in lung cancer.

5. Conclusion

This study presented the benefit of using 4D simulation over 3D simulation in decreasing the PTV with possibly more benefit for smaller size tumors, peripherally located tumors and lower lobe tumors. The use of respiratory gated CT simulation and further prospective studies should be encouraged for developing countries.

Conflict of interest

None declared.

Financial disclosure

None declared.

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